Drug product:	SEROQUEL XR	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate extended release		
Edition No:	Final		
Study code:	D1448C00001		
Date:	21 November 2007		

A Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended-release (SEROQUEL®) as Monotherapy in the Treatment of Patients with Major Depressive Disorder (Moonstone Study)

Study centers

This study was conducted at 47 centers in the United States.

Publications

None at the time of the writing of this report.

Study dates		**Phase of development**
First patient enrolled	28 April 2006	Therapeutic confirmatory (III)
Last patient completed	14 May 2007	

Objectives

The **primary** objective of the study was to evaluate the efficacy of 3 different doses of quetiapine extended-release (XR) versus placebo in patients with major depressive disorder (MDD).

The **secondary** objectives were:

1. To evaluate if quetiapine XR improves the health-related quality of life of patients with MDD, compared to placebo;

2. To evaluate the efficacy of quetiapine XR versus placebo at Day 4 in patients with MDD;

3. To evaluate if quetiapine XR is effective at Day 4 in patients with MDD;

4. To evaluate if quetiapine XR reduces anxiety symptoms in patients with MDD, compared to placebo;

5. To evaluate if quetiapine XR is effective in reducing suicidal ideation in patients with MDD, compared to placebo;

6. To evaluate if quetiapine XR improves sleep quality in patients with MDD, compared to placebo;

7. To evaluate if quetiapine XR improves somatic symptoms in the treatment of patients with MDD, compared to placebo;

8. To evaluate if quetiapine XR improves satisfaction with medication, compared to placebo;

9. To evaluate if quetiapine XR is as safe and well-tolerated as placebo in the treatment of patients with MDD.

An additional objective was to establish a panel of DNA samples from patients who provided separate consent for genetic research in order to enable exploratory studies of genetic factors that may influence drug response. The genetic research was optional for individual patients and centers and is not accounted for in this study report.

Study design

This was a 8-week, multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled Phase III study of the efficacy and safety of quetiapine XR 50 mg/day, 150 mg (3 × 50 mg) per day, and 300 mg/day as monotherapy in the treatment of patients with MDD. This study consisted of an up to 28-day enrollment period, a 6-week randomized treatment period with 1 of 4 treatment regimens (quetiapine XR 50 mg, quetiapine XR 150 mg, quetiapine XR 300 mg, or placebo), and a 2-week post-treatment period.

Target population and sample size

Male and female patients, 18 to 65 years old inclusive, with documented clinical diagnosis using the Mini-International Neuropsychiatric Interview (MINI) and meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) of either 296.2x Major Depressive Disorder, Single Episode, or 296.3x Major Depressive Disorder, Recurrent.

The patients had to have a Hamilton Rating Scale for Depression (HAM-D) score ≥22 to be eligible for the study. The aim of this study was to randomize a patient population with approximately 40% of the patients having a HAM-D score of ≥28.

It was planned to randomly assign 712 patients to obtain a total of 664 evaluable patients (166 per treatment group). The sample size calculation in this study was done to ensure an 80% power in demonstrating superior efficacy of the 150-mg and/or 300-mg quetiapine XR doses over placebo with regard to the primary outcome variable, change in MADRS total score from randomization to Week 6. The appropriate sample size was attained by assuming an anticipated difference of 3.5 unit difference from placebo, with a between-patient variability (standard deviation) of 9 for the change in MADRS total score from baseline to Week 6. Because of multiplicity considerations, a 2-sided test at $\alpha = 0.025$ and a power of 90% for each of the 2 high doses were assumed. This yields a planned sample size of 166 for each of the 4 arms, and 664 in total.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Quetiapine XR 50-mg or 300-mg tablets were orally administered once daily in the evening, in doses of 50 mg, 150 mg, or 300 mg.

Placebo tablets matching quetiapine XR 50-mg tablets and quetiapine XR 300-mg tablets were administered once daily in the evening.

Study treatment was given in tablets of the following doses (lot #): quetiapine 50 mg (9003K, LJ4706, MC4605), quetiapine 300 mg (9049K, 9051K, LM4613), placebo 50-mg match (CE888X, CL879X, CP021X), and placebo 300-mg match (CE891X, CL888X, 73042001FC01).

Duration of treatment

An initial washout period of 7 to 28 days (depending on the medications involved) was followed by a double-blind treatment period for up to 6 weeks (42 days). Eligible patients were randomly assigned to blinded treatment in a 1:1:1:1 ratio to the 50-mg/day quetiapine XR treatment group, the 150-mg/day quetiapine XR treatment group, the 300-mg/day quetiapine XR treatment group, or the placebo treatment group. All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3. Patients in the quetiapine XR 150 mg/day–group maintained this dose through the end of the randomized treatment period. Patients in the quetiapine XR 300-mg/day group were up-titrated to 300 mg/day on Day 5, and then maintained this dose through the end of the randomized treatment period. Following completion of the 6 week randomization period, patients participated in a 2-week post-treatment period. During the post-treatment period, patients were asked to call in to an Interactive Voice Response System (IVRS) to participate in an assessment of discontinuation symptoms assessed by the Treatment Discontinuation Signs and Symptoms (TDSS) scale and return to the study center for 2 post-treatment visits.

Criteria for evaluation (main variables)

The outcome variables are presented in Table S1.

Table S1 Outcome variables

Primary efficacy outcome variable

Change from randomization to Week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

Secondary efficacy variables supporting the primary objective

Change from randomization to each assessment in MADRS total score; MADRS response, defined as a ≥50% reduction from randomization in the MADRS total score at Week 1 and Week 6; MADRS remission, defined as total score ≤8 at Week 6; change from randomization to Week 6 in the HAM-D total score and the HAM-D Item 1 score; change from randomization to Week 6 in Clinical Global Impression –Severity (CGI-S) score; the proportion of patients with Clinical Global Impression – Improvement (CGI-I) score of "much/very much improved" at Week 6.

Secondary variable of particular interest

Change from randomization to Week 6 in Quality of Life Enjoyment Satisfaction Questionnaire (Q-LES-Q) percent maximum total score.

Other secondary efficacy variables

Change from randomization to Day 4 in the CGI-S score, MADRS response, defined as a ≥50% reduction from randomization in the MADRS total score at Day 4; change from randomization to Week 6 in HAM-A total score, HAM-A psychic anxiety subscale score, HAM-A somatic anxiety subscale score, HAM-D anxiety items score, HAM-D sleep disturbance items score, PSQI global score, in MADRS Item 10 score, Q-LES-Q percent maximum total score, Q-LES-Q Item 16, and Q-LES-Q Item 15 scores.

Safety variables

Laboratory values, physical examination, vital signs, weight, BMI, waist circumference, ECG, SAS, BARS, CSFQ, AEs (including EPS-related), TDSS, MADRS Item 10 score ≥4 or an AE related to suicidality, and incidences of suicidality using suicidality analysis.

AE Adverse event. BARS Barnes Akathisia Rating Scale. BMI Body mass index. CGI-I Clinical Global Impression–Improvement. CGI-S Clinical Global Impression–Severity. CSFQ Changes in Sexual Functioning Questionnaire. ECG Electrocardiogram. EPS Extrapyramidal symptoms. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. MADRS Montgomery-Åsberg Depression Rating Scale. PSQI Pittsburgh Sleep Quality Index. Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire. SAS Simpson-Angus Scale. TDSS Treatment discontinuation signs and symptoms.

Statistical methods

All hypotheses were tested with 2-sided tests. Where appropriate, model-based point estimates were presented together with 2-sided 95% confidence intervals. Missing data were imputed using the last observation carried forward (LOCF) approach, as appropriate.

The primary efficacy outcome variable (change in the Montgomery-Åsberg Depression Rating Scale [MADRS] from baseline to Week 6) was analyzed using an analysis of covariance (ANCOVA) model that included baseline MADRS total score as covariate, treatment as fixed effect and center as random effect. The secondary efficacy outcome variable of particular interest (change in the Quality of Life Enjoyment Satisfaction Questionnaire [Q-LES-Q] percent maximum total score from baseline to Week 6) was analyzed the same way as the primary variable. In order to take account of these 6 comparisons and to preserve the overall experimentwise type-I error rate at $\alpha = 0.05$, a tree-structured gatekeeping procedure (Dmitrenko et al 2007) consisting of 3 families of hypotheses was used. This procedure

satisfied the matching restriction that a positive result for the secondary outcome variable with a certain dose was possible only if the result was positive for the primary outcome variable with the same dose. The first family consisted of the 2 hypotheses connected to quetiapine XR 150 mg and 300 mg in the primary variable (MADRS). The second family consisted of the hypothesis connected to quetiapine XR 50 mg in the primary variable (MADRS) together with the 2 hypotheses connected to quetiapine XR 150 mg and 300 mg in the secondary variable (Q-LES-Q). The third family consisted of the hypothesis connected to quetiapine XR 50 mg in the secondary variable (Q-LES-Q). Multiplicity-adjusted p-values corresponding to the tree-gatekeeping procedure were calculated for each of the 6 hypotheses in accordance with Dmitrenko et al 2007, using: (a) the gatekeeping restrictions just described; and (b) uniform weights within each family, ie, the weights 1/2 and 1/2 within family 1, the weights 1/3, 1/3 and 1/3 within family 2, and the single weight 1 within family 3. Each of these 6 adjusted p-values was then compared to α (α=0.05) to determine whether the hypothesis was to be rejected. No correction of multiplicity was applied for any other variables.

Changes from randomization to each assessment in MADRS total score as well as changes from randomization to Week 6 in Q-LES-Q percent maximum total score, HAM-D total scores, HAM-D Item 1 score, Clinical Global Impression – Severity (CGI-S score), HAM for anxiety (HAM-A) total score, HAM-A psychic anxiety subscale score, HAM-A somatic anxiety subscale score, and the Pittsburgh Sleep Quality Index (PSQI) global score were analyzed similarly to the primary objective. MADRS response at Day 4, Week 1, and Week 6 and remission rates at Week 6, as well as the dichotomized Clinical Global Impression – Improvement (CGI-I) score ("much/very much improved" scores as one category vs all other scores as the second category) at Week 6 were analyzed utilizing logistic regression models. Changes from randomization to Week 6 in MADRS Item 10 score, HAM-D anxiety items score, HAM-D sleep disturbance items score, Q-LES-Q overall quality of life (Item 16) score, Q-LES-Q satisfaction with medication (Item 15) score, as well as all safety assessments were presented by descriptive statistics.

The efficacy analyses were based on the modified intention-to-treat (MITT) analysis set (Full Analysis Set), and the safety analyses were done on the data from patients in the safety analysis set.

Patient population

Analysis sets and patient baseline characteristics are presented in Table S2.

Table S2 Analysis sets and patient baseline characteristics

	PLA	QTP50	QTP150	QTP300	Total
Analysis sets					
N (randomized)	184	182	178	179	723
N safety[a]	181	181	176	179	717
N MITT[b]	178	178	168	176	700

Table S2 Analysis sets and patient baseline characteristics

		PLA	QTP50	QTP150	QTP300	Total
N PP		169	163	154	165	651
N TDSS		110	111	101	88	410
Completed 6-week randomized treatment period		134	134	123	120	448
Completed study[c]		95	103	89	85	372
Demographic characteristics (MITT analysis set)						
Sex: n (%)	Male	65 (36.5)	83 (46.6)	64 (38.1)	73 (41.5)	285 (40.7)
	Female	113 (63.5)	95 (54.3)	104 (61.9)	103 (58.5)	415 (59.3)
Age: years	Mean (SD)	40.3 (11.8)	40.6 (11.1)	41.5 (11.7)	40.7 (12.2)	40.7 (11.7)
	Min to max	18 – 65	18 – 63	19 – 65	18 – 64	18 – 65
Race: n (%)	Caucasian	136 (76.4)	131 (73.6)	124 (73.8)	123 (69.9)	514 (73.4)
	Black	35 (19.7)	39 (21.9)	40 (23.8)	44 (25.0)	158 (22.6)
	Oriental	2 (1.1)	2 (1.1)	1 (0.6)	0 (0)	5 (0.7)
	Other	5 (2.8)	6 (3.3)	3 (1.8)	9 (5.1)	23 (3.3)
Baseline disease characteristics (MITT analysis set)						
DSM-IV diagnosis: n (%)						
296.2x MDD, Single Episode		19 (10.6)	22 (12.3)	28 (16.6)	30 (17.0)	99 (14.1)
296.3x MDD, Recurrent		159 (89.3)	156 (87.6)	140 (83.3)	146 (83.0)	601 (85.9)
MADRS	Mean (SD)	30.5 (5.2)	30.9 (4.5)	30.9 (5.0)	30.6 (4.8)	NC
HAM-D	Mean (SD)	25.5 (3.0)	25.6 (3.1)	25.5 (2.9)	25.7 (2.9)	NC
HAM-D Item 1	Mean (SD)	3.1 (0.5)	3.1 (0.4)	3.1 (0.5)	3.1 (0.5)	NC
HAM-A	Mean (SD)	19.3 (4.9)	19.6 (5.5)	19.4 (5.3)	19.7 (5.3)	NC
CGI-S	Mean (SD)	4.5 (0.6)	4.6 (0.6)	4.5 (0.6)	4.5 (0.6)	NC
Q-LES-Q	Mean (SD)	44.5 (15.1)	41.2 (14.4)	40.3 (13.7)	43.7 (14.6)	NC

[a] Number of patients who received at least 1 dose of investigational product.
[b] Number of patients who took at least 1 dose of investigational product and had a randomization MADRS assessment and at least 1 valid MADRS assessment after randomization.
[c] Number of patients who completed randomization phase plus 2-week follow-up period (TDSS).

CGI-S Clinical Global Impression Severity scale. DSM-IV Diagnostic and and Statistical Manual of Mental Disorders, 4th edition. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. MADRS Montgomery-Åsberg Depression Rating Scale. MDD Major Depressive Disorder. MITT Modified intention-to-treat. n Number of patients. N Number of patients in treatment group. NC Not calculated. PLA Placebo. PP Per-protocol. TDSS Treatment discontinuation signs and symptoms.

Efficacy results

The key efficacy results of the study are presented in Table S3.

Table S3 Efficacy results at Week 6 (LOCF, MITT analysis set)

Outcome variable	PLA N=179	QTP50 N=179	QTP150 N=168	QTP300 N=176
MADRS LS mean change from baseline	-11.07	-13.56[a]	-14.50[b]	-14.18[b]
Proportion with ≥50% MADRS response	30.3	42.7[b]	51.2[c]	44.9[c]
Proportion with MADRS remission (total score ≤8)	18.5	25.8	20.8	26.1
HAM-D LS mean change from baseline	-10.93	-12.35	-12.84[a]	-12.65[a]
HAM-D Item 1 LS mean change from baseline	-1.18	-1.34	-1.45[a]	-1.48[a]
HAM-A total score, LS mean change from baseline	-6.64	-8.11[a]	-8.34[b]	-8.20[a]
CGI-S LS mean change from baseline	-1.11	-1.43[a]	-1.50[b]	-1.49[b]
Proportion improved on CGI-I	39.3	52.8[b]	54.2[b]	54.0[b]
Q-LES-Q LS mean change from baseline	12.59	12.50	12.30	11.56

[a] $p<0.05$ comparison with placebo.
[b] $p<0.01$ comparison with placebo.
[c] $p\leq0.001$ comparison with placebo.
CGI-I Clinical Global Impression Improvement scale. CGI-S Clinical Global Impression Severity scale. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LOCF Last observation carried forward. MADRS Montgomery-Åsberg Depression Rating Scale. MITT Modified intention-to-treat. LS Least square. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR. PLA Placebo.
Note: For the analyses of MADRS and Q-LES-Q change from baseline, p-values were adjusted and compared with $\alpha=0.05$ using a tree-gatekeeping testing strategy.

In patients with MDD, all doses of quetiapine XR were superior to placebo in reducing the level of depressive symptoms as demonstrated by the statistically significant change from randomization to Week 6 in the MADRS total score.

Overall, results from the secondary outcome variables supported the primary objective. MADRS total score was improved in all quetiapine groups relative to placebo by Day 4 (p-values relative to placebo: 0.006 for the quetiapine XR 50 mg/day group, <0.001 for the quetiapine XR 150 mg/day group, and <0.001 for the quetiapine XR 300 mg/day group). The quetiapine XR groups demonstrated greater MADRS response, MADRS remission, reduction in the HAM-A total score, and improvement in HAM-A psychic anxiety subscale score in comparison to the placebo group. Improvements in MADRS, HAM-D, HAM-A, and PSQI scores indicated improved sleep quality with quetiapine XR treatment. However, in the evaluation of health-related quality of life as assessed by the Q-LES-Q, the efficacy of quetiapine XR over placebo was not demonstrated.

Safety results

The number (%) of patients who had at least 1 adverse event (AE) in any category is summarized in Table S4. The dosages of 50 mg/day, 150 mg/day, and 300 mg/day of quetiapine XR were generally well tolerated. The overall incidence of AEs was higher in the quetiapine XR treatment groups in a dose-dependent manner. Most AEs were mild to moderate in all treatment groups. Serious AEs (SAEs) were infrequent in all treatment groups. No deaths occurred in the study. Larger proportions of patients in the quetiapine XR groups discontinued due to an AE than did patients in the placebo group and increased in a dose-dependent manner. The incidence of drug-related AEs was higher in the quetiapine treatment groups, in a dose-dependent manner, compared to placebo.

Table S4 Patients who had an adverse event in any category (safety analysis set)

	PLA N=181	QTP50 N=181	QTP150 N=176	QTP300 N=179
Category of adverse event	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any adverse event	126 (69.6)	144 (79.6)	150 (85.2)	158 (88.3)
Serious adverse event	2 (1.1)	1 (0.6)	1 (0.6)	1 (0.6)
Serious adverse event leading to death	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse event not leading to death	2 (1.1)	1 (0.6)	1 (0.6)	1 (0.6)
Drug-related adverse event[a]	86 (47.5)	123 (68.0)	132 (75.0)	141 (78.8)
Adverse events leading to discontinuation	14 (7.7)	16 (8.8)	26 (14.8)	33 (18.4)

[a] As judged by the investigator.
n Number of patients. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine XR.
Note: Patients with multiple events in the same category are counted only once.
Note: Percentages are calculated as n/N*100.

The incidence of common AEs (occurring at an incidence of ≥2% in any treatment group) is shown by preferred term in Table S5.

Table S5 Common (≥2%) adverse events by preferred term (safety analysis set)

	PLA N=181	QTP50 N=181	QTP150 N=176	QTP300 N=179
MedDRA preferred term[a]	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Dry mouth	16 (8.8)	40 (22.1)	66 (37.5)	74 (41.3)
Sedation	11 (6.1)	49 (27.1)	63 (35.8)	55 (30.7)
Somnolence	20 (11.0)	33 (18.2)	35 (19.9)	52 (29.1)
Headache	27 (14.9)	22 (12.2)	24 (13.6)	26 (14.5)
Dizziness	10 (5.5)	16 (8.8)	19 (10.8)	19 (10.6)

Table S5 Common (≥2%) adverse events by preferred term (safety analysis set)

MedDRA preferred term[a]	PLA N=181 n (%)	QTP50 N=181 n (%)	QTP150 N=176 n (%)	QTP300 N=179 n (%)
Constipation	5 (2.8)	13 (7.2)	15 (8.5)	16 (8.9)
Nausea	11 (6.1)	14 (7.7)	15 (8.5)	16 (8.9)
Insomnia	14 (7.7)	9 (5.0)	12 (6.8)	12 (6.7)
Vomiting	4 (2.2)	3 (1.7)	4 (2.3)	12 (6.7)
Fatigue	8 (4.4)	11 (6.1)	14 (8.0)	11 (6.1)
Back pain	4 (2.2)	3 (1.7)	10 (5.7)	9 (5.0)
Increased appetite	7 (3.9)	8 (4.4)	9 (5.1)	8 (4.5)
Vision blurred	2 (1.1)	3 (1.7)	3 (1.7)	8 (4.5)
Sluggishness	2 (1.1)	4 (2.2)	3 (1.7)	7 (3.9)
Diarrhea	16 (8.8)	12 (6.6)	11 (6.3)	6 (3.4)
Irritability	7 (3.9)	11 (6.1)	10 (5.7)	6 (3.4)
Upper respiratory tract infection	7 (3.9)	6 (3.3)	3 (1.7)	6 (3.4)
Arthralgia	5 (2.8)	3 (1.7)	5 (2.8)	5 (2.8)
Asthenia	2 (1.1)	7 (3.9)	2 (1.1)	5 (2.8)
Dizziness postural	2 (1.1)	3 (1.7)	1 (0.6)	5 (2.8)
Dyspepsia	5 (2.8)	4 (2.2)	10 (5.7)	5 (2.8)
Abdominal distension	0 (0)	0 (0)	0 (0)	4 (2.2)
Disturbance in attention	0 (0)	1 (0.6)	1 (0.6)	4 (2.2)
Hypoaesthesia	0 (0)	0 (0)	1 (0.6)	4 (2.2)
Myalgia	3 (1.7)	8 (4.4)	13 (7.4)	4 (2.2)
Weight increased	1 (0.6)	2 (1.1)	5 (2.8)	4 (2.2)
Abnormal dreams	7 (3.9)	3 (1.7)	4 (2.3)	3 (1.7)
Akathisia	0 (0)	0 (0)	4 (2.3)	3 (1.7)
Restless legs syndrome	0 (0)	3 (1.7)	4 (2.3)	3 (1.7)
Tremor	3 (1.7)	5 (2.8)	3 (1.7)	3 (1.7)
Musculoskeletal stiffness	1 (0.6)	5 (2.8)	2 (1.1)	2 (1.1)
Nasopharyngitis	5 (2.8)	3 (1.7)	6 (3.4)	2 (1.1)
Paresthesia	0 (0)	2 (1.1)	4 (2.3)	2 (1.1)
Pharyngolaryngeal pain	0 (0)	3 (1.7)	4 (2.3)	2 (1.1)
Suicidal ideation	4 (2.2)	2 (1.1)	1 (0.6)	2 (1.1)
Cough	3 (1.7)	5 (2.8)	0 (0)	1 (0.6)
Hypersomnia	0 (0)	1 (0.6)	4 (2.3)	1 (0.6)
Lethargy	1 (0.6)	3 (1.7)	4 (2.3)	1 (0.6)
Palpitations	4 (2.2)	2 (1.1)	3 (1.7)	1 (0.6)

Table S5 Common (≥2%) adverse events by preferred term (safety analysis set)

MedDRA preferred term[a]	PLA N=181 n (%)	QTP50 N=181 n (%)	QTP150 N=176 n (%)	QTP300 N=179 n (%)
Blood pressure increased	1 (0.6)	4 (2.2)	2 (1.1)	0 (0)
Feeling abnormal	0 (0)	1 (0.6)	4 (2.3)	0 (0)
Pollakiuria	4 (2.2)	2 (1.1)	3 (1.7)	0 (0)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
MedDRA Medical Dictionary of Regulatory Activities. n Number of patients. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine XR.
Note: Common adverse event is defined as an event occurring at an incidence of ≥2% in any treatment group.
Note: Events sorted by decreasing frequency in the QTP300 treatment group.
Note: Percentages are calculated as n/N*100.

The pattern of common AEs observed in the quetiapine XR treatment groups generally conformed to that which was anticipated based on the known pharmacological profile of quetiapine. The most common AEs in the quetiapine XR groups were dry mouth, sedation, somnolence, headache, and dizziness, and generally occurred at a higher incidence compared to placebo.

The most common AEs potentially related to extrapyramidal symptoms (EPS) were akathisia, restlessness, extrapyramidal disorder, and tremor. Overall, the assessment of parkinsonian and akathisia symptoms as assessed by Simpson-Angus Scale (SAS) total scores and Barnes Akathisia Rating Scale (BARS) global assessment scores indicated that quetiapine XR treatment was similar to placebo, and an improvement or no worsening in symptoms was noted in most patients in all active treatment groups at the end of treatment.

The incidence of AEs related to suicidality was low in all treatment groups. There was no clinical evidence to suggest a relationship between quetiapine XR treatment and increased suicidality. A higher percentage of patients in the placebo group had a MADRS suicidal thoughts (Item 10) score of ≥4 (placebo group: 3.9%, quetiapine XR 50-mg/day treatment group: 2.2%, quetiapine XR 150-mg/day treatment group: 2.9%, and quetiapine XR 150-mg/day treatment group: 0.6%).

Overall, the clinical laboratory results were consistent with those from previous studies in patients treated with quetiapine for other disorders. No notable differences among the treatment groups in changes from baseline were observed for any hematology assessments. The most notable changes in clinical chemistry parameters involved lipid parameters, including an increase in triglycerides in the quetiapine XR 150-mg and 300-mg groups compared to placebo and quetiapine XR 50-mg groups.

Mean insulin values were increased from baseline in the quetiapine XR 50-mg/day and 300-mg/day groups relative to placebo, but not the quetiapine XR 150-mg/day group. The incidence of AEs that could potentially be related to diabetes was low and equally distributed

among the placebo and quetiapine XR groups; all were of mild or moderate intensity. The incidence of patients with a treatment emergent shift from <3 to ≥3 metabolic risk factors was similar across the 4 treatment groups. There were no cases of treatment-emergent hypothyroidism based on clinically important high thyroid-stimulating hormone (TSH) values in combination with clinically important low thyroxine (T4) values; no AEs of hypothyroidism were reported.

A small increase in mean pulse rate, confirmed by electrocardiographic (ECG) measurement of heart rate, was observed in the quetiapine XR groups. Combined criteria for orthostatic changes in pulse and systolic blood pressure did not show any differential effect of quetiapine XR administration compared to placebo. Mild prolongation of the PR and QT intervals were noted in some patients in the quetiapine XR groups by ECG. No AEs potentially related to QT prolongation occurred during the study.

Based on the change from baseline to the end of treatment in the Changes in Sexual Functioning Questionnaire (CSFQ) total score, sexual functioning improved slightly in all 4 treatment groups. The percentages of patients with a ≥7% weight increase between baseline and the end of treatment was higher in the quetiapine XR 150-mg/day and 300-mg/day treatment groups than the quetiapine XR 50-mg/day and placebo groups. Mean weight gain after randomization was small across all treatment groups (≤1.0 kg).